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(54) Title: ANTITUSSIVE MICROCAPSULES (57) Abstract The present invention relates to compositions for use in the treatment of cough and/or sore throat in the form of microcapsules.		

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ANTITUSSIVE MICROCAPSULES

TECHNICAL FIELD

The present invention relates to compositions for use in the treatment of cough and/or sore throat in the form of microcapsules.

BACKGROUND OF THE INVENTION

The cough reflex is an important mechanism whereby secretions from the lungs and airways are removed. Generally, such secretions are removed by the mucociliary escalator. However, when this mechanism is defective, or becomes overwhelmed by, for example, excessive secretions, cough then becomes a principal means of secretion removal.

The cough reflex is initiated by stimulation of mechanical receptors and is controlled by afferent pathways within the vagus (X), glossopharyngeal (IX), and superior laryngeal nerves to the cough center in the brainstem. Cough can be caused by, for example, foreign bodies, dust, mucus, debris, gases and smoke in the lower respiratory tract. Irritation of various sensory nerves in the nose, sinuses, pharynx, ears, stomach, pericardium or diaphragm can also produce coughing. In many of these conditions, chronic or paroxysmal cough, however, can be exhausting and debilitating, particularly when it interferes with sleep.

Oral cough preparations, such as tablets, lozenges, syrups, solutions, suspensions and the like, containing an effective antitussive agent have long been used for the symptomatic relief of coughs. The most popular of such preparations contain either dextromethorphan (or its hydrobromide salt) or codeine (or its sulfate salt) as the active antitussive agent. These treatments, among many others, are fully described in Drug Evaluations, 6th Ed., Chapter 21 (The American Medical Association, 1986).

Generally, cough syrups and sore throat medications have been available as pourable liquids or thixotropic gels. Exemplary prior art gel formulations for treatment of cough including those disclosed in U.S. Patent 4,427,681, incorporated herein by reference which use a suspending agent (Avicel/R R-591 from FMC Corporation) that give a thixotropic character to the formulation that is very viscous and needs a special device or an appropriate amount of shear forces through a dispensing nozzle to pour.

Other formulations include liquid gelatin capsules which are well-known; however, they are intended to be swallowed and thereby do not provide any coating of the oral mucosa. Other liquid gelatin capsules which are intended to be bitten have thick gelatin shells which either dissolve slowly or need to be expectorated after release of the actives or when the user doesn't want the capsule in the mouth any longer. U.K. Patent 1,060,258 discloses pastilles having a thick outer gelatin layer containing an active which are sucked or chewed until an active in the core released. The remaining gelatin shell is then chewed in the mouth until dissolved. Such conventional gelatin capsules also have seams which create problems such as leakage and are also less aesthetically pleasing.

Due to the nature of the action of the active ingredients in the present invention, Applicants have found that it is highly desirable to have microcapsule compositions which contain an antitussive and/or anesthetic active which are portable and easy to use and which rupture rapidly upon biting or sucking and wherein the outer shell dissolves quickly (avoiding further irritation) thereby providing the user a quick delivery of an active ingredient to the irritated area.

It is, therefore, an object of the present invention to provide improved microcapsules. It is still a further object of the present invention to provide such compositions which can treat the irritation, pain and discomfort associated with laryngopharyngitis and esophagitis. A further object of the present invention is to provide such microcapsule compositions containing a pharmaceutical active which is delivered quickly to the oral mucosa. These and other objects of this invention will become apparent in light of the following.

SUMMARY OF THE INVENTION

The present invention in one of its aspects relates to improved microcapsules which contain an antitussive and/or anesthetic active.

All percentages and ratios used herein are by weight unless otherwise specified. Additionally, all measurements are made at 25°C unless otherwise specified.

DETAILED DESCRIPTION OF THE INVENTION

The essential as well as optional components of the capsules of the present invention are described in the following paragraphs.

Capsule Shell Material:

The shell material of the microcapsules of the present invention can

be any materials which are suitable for ingestion as well as retention in the oral cavity. Materials which are suitable include gelatin, polyvinyl alcohols, waxes, gums, sucrose esters and sugar candy type materials used in cough drops and mints, for example.

The shell material is used to form any of a wide variety of shapes such as spheres, oblong shapes, disks, puffed squares and cylinders. The shell thickness is in the range of about 30 μ m to about 0.5mm, preferably from about 30 μ m to about 0.3mm. If the microcapsules are spherical, the particle diameter is generally in the range of from about 2mm to about 9mm, preferably from about 3mm to about 7mm. The shells also have a water content of about 10% or greater, preferably 12% or greater and most preferably 15% or greater.

The microcapsules made according to the present invention ruptures within about 45 seconds, preferably within about 35 seconds, more preferably within about 30 seconds and most preferably within about 25 seconds and dissolves within about 5 minutes, preferably within about 4 minutes and most preferably within about 3.5 minutes (USP Methodology XXII Method 701 "Disintegration").

Antitussive/Anesthetic Active:

The antitussives preferred for use in the present invention include those such as dextromethorphan, chlorphedianol, carbetapentane, caramiphen, noscapine, diphenhydramine, codeine, hydrocodone, hydromorphone, fominoben, benzonatate, their pharmaceutically-acceptable salts, and mixtures thereof. The oral anesthetics preferred for use include phenol, lidocaine, dyclonine, benzocaine, menthol, benzyl alcohol, salicyl alcohol, and hexylresorcinol, their pharmaceutically-acceptable salts, and mixtures thereof.

The compositions of the present invention can also include at least one additional oral pharmacological active preferably selected from the following classes: (a) analgesic agents, (b) decongestants, (c) expectorants and (d) antihistamines. The analgesics useful for this invention include acetaminophen, acetyl salicylic acid, indomethacin and optically active isomers or racemates of ibuprofen, naproxen, flurbiprofen, carprofen, tiaprofenic acid, cicloprofen, ketoprofen, ketorolac, etodolac, indomethacin, sulindac, fenoprofen, diclofenac, piroxicam, benzydome, nabumetone, their pharmaceutically acceptable salts and mixtures thereof. The decongestants prepared for use in the compositions of the present

invention include pseudoephedrine, phenylpropanolamine, phenylephrine and ephedrine, their pharmaceutically acceptable salts, and mixtures thereof. The preferred anesthetics include glyceryl guaiacolate, terpin hydrate, ammonium chloride, N acetylcysteine and bromhexine, ambroxol, their pharmaceutically acceptable salts, and mixtures thereof. All of these components, as well as their acceptable dosage ranges are described in the following: U.S. Patent 4,783,465 to Sunshine et al., issued November 8, 1988, U.S. Patent 4,619,934 to Sunshine et al., issued October 28, 1986, which are incorporated by reference herein.

Also useful are bronchodilators such as terbutaline, aminophylline, epinephrine, isoprenaline, metaproterenol, bitoterol, theophylline and albuterol. A highly preferred optional component is caffeine.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from nonorganic bases include sodium, potassium, lithium, ammonia, calcium, magnesium, ferrous, zinc, manganous, aluminum, ferric, manganic salts and the like. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, tertiary and quaternary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as triethylamine, tripropylamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, lysine, arginine, histidine, caffeine, procaine, N-ethylpiperidine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglycine, theobromine, purines, piperazine, piperidine, polyamine resins and the like.

Methods

The amount of the pharmaceutical composition administered depends upon the percent of active ingredients within its formula, such as an analgesic, decongestant, cough suppressant, expectorant, antihistamine and/or gastrointestinal active required per dose, stability, release characteristics and other pharmaceutical parameters.

Usually from about 1 mg/kg to about 500 mg/kg per day, preferably from about 5 mg/kg to about 300 mg/kg per day and most preferably from about 5 mg/kg per day to about 200 mg/kg per day of the pharmaceutical composition is administered as described herein. This amount can be given in a single dose, or, preferably, in multiple (two to six) doses repeatedly or sustained release dosages over the course of treatment.

Generally, each individual dosage of the pharmaceutical compositions of the present invention range from about 1 mg/kg to about 25 mg/kg, preferably from about 2 mg/kg to about 15 mg/kg and most preferably from about 3 mg/kg to about 10 mg/kg. While dosages higher than the foregoing may be effective, care must be taken, as with any drug, in some individuals to prevent adverse side effects.

The following examples illustrate embodiments of the subject invention wherein both essential and optional ingredients are combined.

These pharmaceutical agents are used in an amount of from about 0.1% to about 50%.

Dispersed within the shell material may be the same agents at the same concentrations.

Diluents for Use in Microcapsule Core:

The solubilizing agent for the antitussive and/or anesthetic agents used in the cores of the present microcapsules can be any of a number of materials.

Although water itself may make up the entire carrier, typical liquid formulations preferably contain a co-solvent, for example, propylene glycol, corn syrup, glycerin, sorbitol solution and the like, to assist solubilization and incorporation of water-insoluble ingredients, such as flavoring oils and the like into the composition. In general, therefore, the compositions of this invention preferably contain from about 1 to about 70%v/v and, most preferably, from about 5 to about 50% v/v, of the co-solvent. Preferred are oils such as corn, olive, rapeseed, sesame, peanut or sunflower. Other preferred materials are triglycerides such as Captex 300 and polyethylene glycols such as PEG 400. These are used in an amount of from about 20% to about 80%, preferably from about 35% to about 70% of the total capsule weight.

In addition, the present invention may optionally incorporate a cooling agent or a combination of cooling agents. Suitable cooling agents include, for example, menthol as well as those described in U.S. Patent 4,136,163, January 23, 1979, to Watson et al., U.S. Patent 4,230,668, October 28, 1980, to Rowsell et al. and U.S. Patent 4,032,661, to Rowsell et al., all of which are herein incorporated by reference. A particularly preferred cooling agent is N-ethyl-p-menthane-3-carboxamide (WS-3 supplied by Sterling Organics), taught by the above incorporated U.S. Patent

4,136,163. Another particularly preferred cooling agent is 3-1-menthoxypropane 1,2-diol (TK-10 supplied by Takasago Perfumery Co., Ltd., Tokyo, Japan). This material is described in detail in U.S. Patent 4,459,425, July 10, 1984 to Amano et al. and incorporated herein by reference.

Other optional ingredients well known to the pharmacist's art may also be included in amounts generally known for these ingredients, for example, natural or artificial sweeteners, flavoring agents, colorants and the like to provide a palatable and pleasant looking final product, antioxidants, for example, butylated hydroxy anisole or butylated hydroxy toluene, and preservatives, for example, methyl or propyl paraben or sodium benzoate, to prolong and enhance shelf life.

Additional Agents Suitable for Use in the Core of Capsule:

The core of the microcapsules of this invention may contain any number of additional materials to provide additional efficacy and/or sensory perceptions. Such agents may include flavoring agents such as thymol, eucalyptol, menthol, methyl salicylate or witch hazel. These agents are used in an amount of from about .1% to about 25%, preferably from about 5% to about 15% of the total capsule weight.

In addition, a variety of sweetening agents such as sugars, corn syrups, saccharin or aspartame may also be included in the core. These agents are used in an amount of from about .1% to about 5%, preferably from about .35% to about 1.5% of the total capsule weight.

Method of Manufacture:

The capsules of the present invention can be made using a variety of techniques. One method is described after the following examples.

Industrial Applicability:

The capsules of the present invention are used by placing the capsules into the mouth which then rupture rapidly upon biting or sucking and wherein the outer shell dissolves quickly (avoiding further irritation) thereby providing the user a quick delivery of an active ingredient to the irritated area.

The following examples further describe and demonstrate preferred embodiments within the scope of the present invention. The examples are given solely for the purposes of illustration and are not to be construed as illustrative of limitations of this invention. Many variations thereof are possible without departing from the invention's spirit and scope.

EXAMPLES 1-5

The following compositions/capsules are representative of the present invention.

<u>Component</u>	<u>Weight %</u>				
	<u>1(6mm)</u>	<u>2(9mm)</u>	<u>3(9mm)</u>	<u>4(9mm)</u>	<u>5(9mm)</u>
Gelatin	7.420	9.486	8.345	9.332	8.679
Sorbitol Solution	2.561	3.268	2.941	2.560	2.340
(70% Aqueous, Ex. 1-2; Crystalline, Ex. 4-5)					
Saccharin	0.555	0.423	0.542	0.460	0.363
Acetosulfame	1.455	1.202	1.626	1.579	1.321
Aspartyl phenyl alanine methyl ester	0.654	0.500	-	0.577	0.647
Monoammonium glycyrrhizin	0.042	0.060	-	0.027	0.040
Neohesperidin dihydrochalcone	-	0.020	-	0.030	-
FD&C Blue #1	0.010	0.010	0.020	0.015	0.014
FD&C Yellow #5	0.005	0.005	-	-	0.007
Captex 300	8.678	8.453	8.547	8.322	8.255
Flavor	5.761	7.245	7.247	8.267	7.239
Citric Acid	-	-	-	0.259	-
Dextromethorphan hydrobromide	3.846	3.409	6.818	6.818	6.818
Benzocaine	0.962	-	-	-	0.962
Propylene Glycol	2.078	-	2.078	-	2.016
Glycerin	0.412	-	0.412	0.273	0.399
Pseudoephedrine HCl	-	-	-	-	6.818
Dyclonine HCl	-	-	2.045	2.045	-
Chlorpheniramine Maleate	-	-	-	0.909	-
Polyethylene glycol 400	26.847	27.516	22.909	23.294	18.144
Sucrose Acetate	34.714	33.785	33.910	31.548	33.020
Isobutyrate					
Water	4.000	4.618	2.560	3.685	2.951

1) Captex 300 is a triglyceride supplied by Capitol City Product, Columbus, Ohio.

- 2) This amount includes that in the gelatin shell as well as in the core.

The above compositions are prepared by mixing the components of the core in one container and the components of the shell(s) in another container. The shell(s) materials are heated to provide a fluid medium. The core and shell(s) materials are then pumped separately to a two or three fluid nozzle submerged in an organic carrier medium. The capsules formed are allowed to cool and stiffen. They are then dried and separated for further handling.

In the above compositions any of a wide variety of other shell materials, optional pharmaceutical active agents, sweeteners as well as other components may be used in place of or in combination with the components listed above.

WHAT IS CLAIMED IS:

Claims:

1. A microcapsule suitable for use in the mouth and ingesting for use in the treatment of cough and/or sore throat comprising:
 - a) an outer shell having a wall thickness of from 30 μ m to 0.5 mm, wherein said shell has a water content of 10% or greater; and
 - b) a core composition comprising an oral pharmaceutical active selected from the group consisting of antitussives and anesthetics and mixtures thereof.
2. A microcapsule according to Claim 1 wherein the shell material is gelatin.
3. A microcapsule according to any one of the preceding Claims wherein said microcapsule ruptures within 45 seconds and dissolves within 5 minutes, preferably within 35 seconds and dissolves within 4 minutes
4. A microcapsule according to any one of the preceding Claims wherein said antitussive is selected from the group consisting of dextromethorphan, chlorphedianol, carbetapentane, caramiphen, noscapine, diphenhydramine, codeine, hydrocodone, hydromorphone, fominoben, benzonatate, their pharmaceutically-acceptable salts, and mixtures thereof and wherein said oral anesthetic is selected from the group consisting of phenol, lidocaine, dyclonine, benzocaine, menthol, benzyl alcohol, salicyl alcohol, and hexylresorcinol, their pharmaceutically-acceptable salts, and mixtures thereof.
5. A microcapsule according to any one of the preceding Claims wherein the shell has a wall thickness of from 30 μ m to 0.3 mm.
6. A microcapsule according to any one of the preceding Claims wherein the shell has a water level of greater than 12%.

7. A microcapsule according to any one of the preceding Claims wherein the microcapsules are in the form of spheres having a diameter of from 2mm to 9mm.
8. A microcapsule according to any one of the preceding Claims which further comprises a pharmaceutical active selected from the group consisting of analgesics, decongestants, expectorants and antihistamines and mixtures thereof.
9. A microcapsule according to any one of the preceding Claims wherein the microcapsules are made using a three fluid nozzle.

INTERNATIONAL SEARCH REPORT

Inter. Nat. Application No.
PCT/US 96/02238

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K9/48 A61K9/50 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,93 11754 (THE PROCTER & GAMBLE COMPANY) 24 June 1993 see page 2, line 22 - line 34; claims 1-10 see page 3, line 25 ---	1-9
Y	US,A,4 935 243 (LIONEL BORKAN ET AL.) 19 June 1990 see column 2, line 22 - line 47 see column 3, line 59 - line 63 ---	1-9
Y	US,A,5 084 278 (ATUL M. MEHTA) 28 January 1992 see column 2, line 5 - line 37; claims 1,6 ---	1-9
Y	US,A,4 656 027 (ROLF I. SJÖÖVIST) 7 April 1987 see claims 1,3 --- -/-	1-9

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Inter- nal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>W0,A,91 03236 (UNIVERSITY OF UTAH RESEARCH FOUNDATION) 21 March 1991 see page 1, paragraph 1 see page 16, line 20 - page 17, line 9 see page 19, line 1 - line 15 see page 26, line 22 - line 32 see page 39, line 12 ---</p>	1-9
Y	<p>GB,A,1 060 258 (SANDOZ PRODUCTS LIMITED) 1 March 1967 cited in the application see page 1, line 19 - page 2, line 48 -----</p>	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

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